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Original Research Article

The radiation dose tolerance of the brachial plexus: A systematic review and meta-analysis

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ABSTRACT

Purpose: We performed a systematic review and meta-analysis of studies reporting the incidence of radiation induced brachial plexopathy (RIBP) and the associated radiotherapy doses to this structure.
Methods: Databases were queried without language restriction for cohort studies reporting RIBP incidence and associated brachial plexus dose maximum dose (bpDmax). Studies specifying RIBP relative risk (RR) effect size were selected for meta-analysis. RRs for RIBP from each study were converted to a regression coefficient (β) and standard error corresponding to a continuous representation of bpDmax. The adjusted β from individual studies were combined using a random effects model and weighted by inverse variance ($1/SE^2$). The trim and fill approach was used to assess publication bias.
Results: We identified 25 studies that included 37 unique patient cohorts eligible for analysis. Seventeen cohorts experienced an RIBP incidence ≤5%, of which 6 cohorts exceeded conventional plexus constraints of 60 Gy for bpDmax. Five of the 6 cohorts were simulated with 3D-CT techniques. Meta-analysis of eligible studies demonstrated a significant increase in RIBP risk for each Gy increase in bpDmax (RR, 1.11; 95% CI 1.07–1.15). Results remained significant after adjustment for publication bias and when sensitivity analysis was performed.
Conclusions: Our results suggest that current brachial plexus constraints of 60–66 Gy are safe. Meta-analysis provides a log-linear model to quantify the association of brachial plexus dose and RIBP risk, and thus inform the therapeutic ratio for dose escalation. Further prospective studies reporting dosimetric data can better refine this model and inform brachial plexus constraint guidelines.

1. Introduction

Damage to the brachial plexus can arise following surgery or radiation. Brachial plexopathy manifests clinically as neuropathic pain, paresthesias, or motor weaknesses of the upper extremities, and can cause significant morbidity [1]. Radiation induced brachial plexopathy (RIBP) is a late toxicity that can present months to years following a course of radiotherapy [2]. Biopsy studies have shown that the mechanisms of RIBP include peri-plexal soft tissue fibrosis as well as direct demyelination [3–5]

Classically, the dose tolerance as defined by Emami for the brachial plexus is 62 Gy, 61 Gy, and 60 Gy to one third, two thirds, and the whole plexus volume respectively, for a 5% risk of RIBP at 5 years [6]. The QUANTEC studies, which aimed to provide updated tolerances in light of radiotherapy advancement, did not specify guidelines for brachial plexus dose tolerance [7]. In Emami's recent update, the dose tolerance for the brachial plexus remained at 60 Gy, but is now defined as a maximum point dose to reflect the serial nature of the plexus as an organ [8]. Modern RTOG constraints vary between 60 Gy and 66 Gy maximum point doses [9–12].

The supporting evidence for these recommendations is scarce however and is derived from a small number of observational studies that comprise the basis of these widely accepted clinical guidelines. Furthermore, many of these studies are older and utilize non-CT based, 2D planning techniques, possessing dosimetric uncertainty [5,13,14]. There is some evidence to suggest that the dose tolerance may be even higher than those currently recommended [15–17]. If this is the case, radiotherapy plans may jeopardize local control if the prescribed dose is constrained by the current tolerance guidelines [17,18].

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The purpose of this literature review was to synthesize the existing evidence that describes brachial plexopathy risk in response to radiation dose. We aimed to compare literature data with current dose constraint guidelines and develop a model associating brachial plexus dose and RIBP risk.

2. Methods

2.1. Search strategy

A literature search was performed using Medline, EMBASE, and CINAHL databases for full journal articles or abstracts without language restriction from inception to February 5, 2018. The searches each combined relevant keywords and medical subject headings (MeSH) with minor variations specific to each database. Database searches were supplemented by manual searching of journal references (Appendix A).

Articles were included if they were full journal articles or abstracts that described the incidence of brachial plexopathy in a cohort of patients receiving radiotherapy in which the brachial plexus was within the radiation field. All cohorts had a minimum of 10 patients. Studies included patients with cancer from any disease site, radiotherapy technique, dose fractionation schedule, or treatment intent. No restrictions were placed on patient cohorts receiving other oncologic treatments (ie. surgery or systemic therapy).

Studies were excluded if the dose absorbed by the brachial plexus was not stated explicitly, the radiotherapy schedule was irregular, or if the patients received previous radiotherapy dose to the brachial plexus. Reviews, commentaries, and letters were excluded.

2.2. Data extraction and analysis

Search results were imported into Covidence (Veritas Health Innovation, Melbourne, Australia) for determination of eligibility. Data pertaining to patient characteristics, treatment eras, radiotherapy schedules, radiotherapy techniques, brachial plexus doses, brachial plexopathy incidences, and use of systemic therapy were extracted onto a data extraction form. In studies that described separate patient cohorts, each cohort was extracted as an independent data set. The maximum brachial plexus dose (bpDmax) was used to define the radiotherapy dose absorbed by a cohort. In the case where a range of bpDmax was reported, the mean as defined by the study was used. In studies where the median bpDmax was reported, conversion to mean and estimated standard deviation were performed utilizing previously described methods [19]. All doses were converted into corresponding equivalent dose in 2 Gy fractions (EQD2) doses using the linear quadratic formula, assuming an alpha/beta of 3 for the brachial plexus [20]. EQD2 doses were plotted against the incidence of RIBP and stratified by planning methodology.

Two-dimensional (2D) planning was defined as patients who underwent planning using X-ray radiographs and clinical markup. In contrast, 3D planning was defined for patients who were planned using CT-based simulation. Image-guided radiotherapy (IGRT) refers to the subset of patients who were 3D planned and received image-guided verification prior to each radiotherapy fraction delivered. IGRT techniques include 3D-conformal radiotherapy (3D-CRT), intensity modulated radiotherapy (IMRT), volumetric modulated arc radiotherapy (VMAT), and stereotactic body radiotherapy (SBRT).

2.3. Dose- risk estimation and meta-analysis

Studies that reported a specific RIBP effect size as a function of absorbed brachial plexus were selected for meta-analysis. Synthesis of the data was challenging because eligible studies reported a combination of categorical and/or continuous effect size estimates that were presented as risk ratios, odds ratios, or hazard ratios. In order to homogenize effect size representations to facilitate synthesis, all categorical representations were converted to a regression coefficient (β) and standard error corresponding to a continuous representation for each Gy increase in bpDmax as described previously [21].

This conversion of categorical reported data was done by determining a central value of RIBP effect for each category within the included studies. Study text and/or figures were used to determine the categorical ranges and associated central values. Regression coefficients were calculated as $\log(RR)/(x_n\text{-}x_0)$, where x_n denotes the dose at group n level, and x_0 denotes the dose at reference group. Similarly, the standard error (SE) was calculated as $(\log[\text{upper CI}] - \log[\text{lower CI}])/([x_n\text{-}x_0]*3.92)$, where CI is confidence interval. The reference group in studies with categorical representations of RIBP effect corresponds to the group that received the lower radiotherapy dose. The estimates produced by these methods are only relevant for the range of bpDmax covered in the underlying studies, and there is a log-linear relationship assumed between the effect estimate and dose.

The regression coefficients from individual cohorts were combined using a random-effects model. The inverse variance ($1/SE^2$) was used to weight individual studies. Analysis was done for RIBP incidence. The homogeneity assumption was assessed by the Cochran X^2 statistic, and the I^2 statistic was calculated. The statistical analyses were performed using R package meta-analysis version 3.5–0 (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed $P < 0.05$ was considered statistically significant.

Publication bias was analyzed using standard error-based funnel plots as described by Egger et al. [22]. Additionally, the trim and fill approach was used to obtain an adjusted effect size that takes into account publication bias [23]. Sensitivity analysis was performed by systematically removing each study sequentially, and calculating a combined effect size from the remaining studies.

3. Results

3.1. Literature search

Our systematic search returned 2675 articles to screen for analysis. After removing duplicates, and adding 5 hand-searched articles, 1983 studies were selected for title and abstract screening, with 163 moving to full text screening. Ultimately, 25 studies met the inclusion criteria for our review, with 37 distinct patient subgroups extracted and 4227 brachial plexuses at risk. Most studies were full journal articles, apart from 4 abstracts (Fig. 1). Only one study was prospective. All studies, with the exception of one Italian study, were in English. Study publication years ranged from 1966 to 2017, with 16 studies published in the year 2000 or later.

3.2. Patient characteristics

Patient characteristics are reported in Table 1. The mean age of all patient cohorts, where made available was 56.9 (range 49–78). The median cohort size was 67 (range 10–582). The most common disease site was breast, followed by head and neck. Nineteen cohorts from 11 studies were planned using 2D techniques. Eighteen cohorts from 14 studies underwent 3D CT-based planning. Of the latter cohorts, all were treated with IGRT including 3D-CRT, IMRT, VMAT, and SBRT, with the exception of one study that used clinical setup in the treatment of breast cancer patients [24].

For all cohorts, the median time to onset of plexopathy post radiotherapy, where reported, was 7 months (range 4.5–

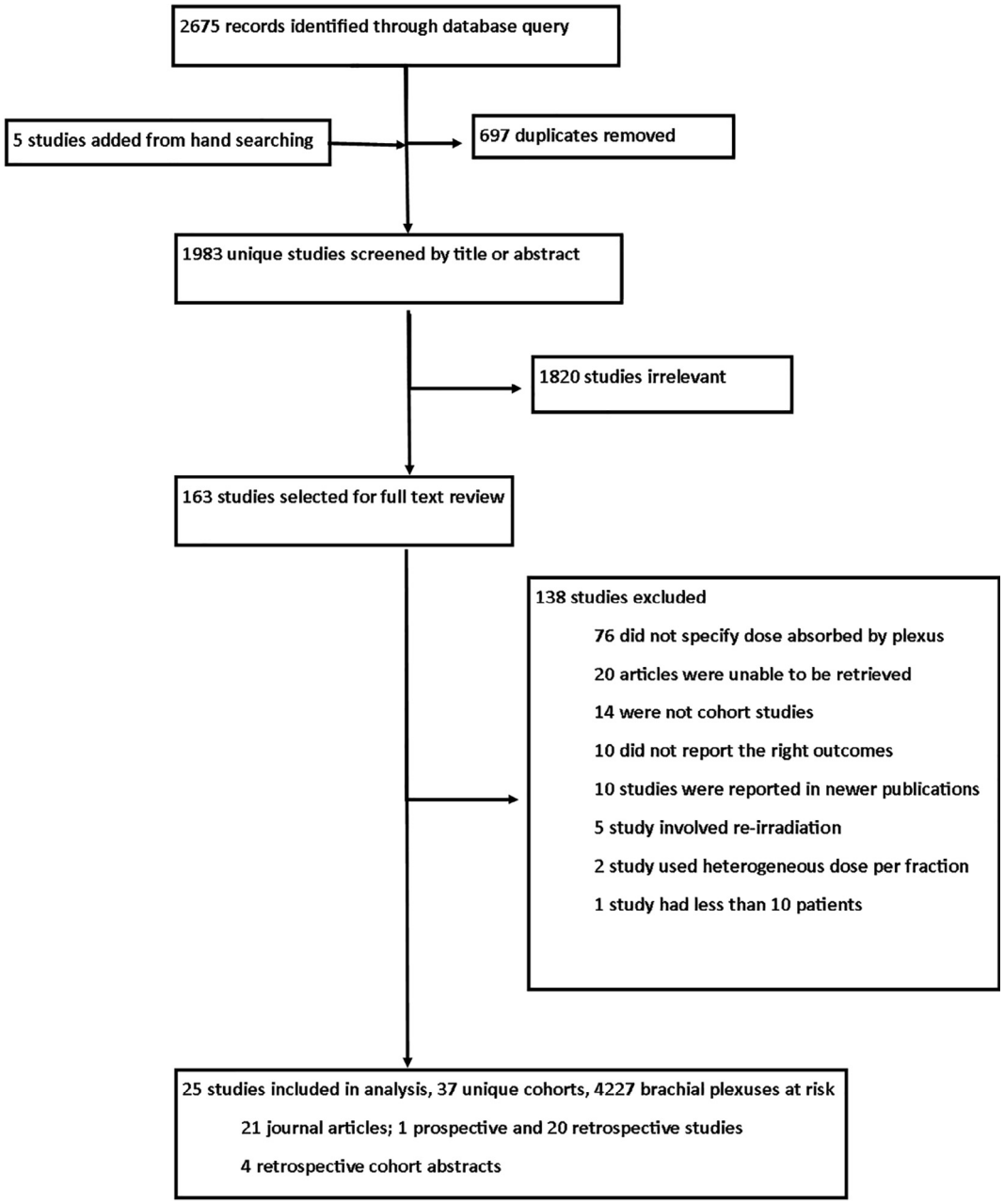

Fig. 1. PRISMA diagram. A total of 1983 studies were screened, with 163 articles selected for full text review. A total of 25 studies were included in the review.

88 months). The median length of follow up, where reported, was 40 months (range 13–408 months). Chemotherapy usage was more common in the 3D-CT simulated cohorts.

3.3. Dose to brachial plexus and brachial plexopathy incidence

The maximum brachial plexus dose, the dose in EQD2, dose per fraction and the incidence of RIBP in patients planned with 2D and 3D-CT simulation are displayed in Tables 2A and 2B respectively.

The mean bpDmax to the brachial plexus in EQD2 was 71.2 Gy in the 2D simulated cohorts and 65.8 Gy in the 3D cohorts. The median RIBP incidence was 14% and 5.6% in these same groups.

EQD2 doses were plotted against RIBP incidence for all 37 study cohorts (Fig. 2). A total of 16 cohorts experienced an RIBP incidence of $\leq$5%. Of these, 10 cohorts received a bpDmax EQD2 $\leq$60 Gy, and 12 received a bpDmax EQD2 $\leq$66 Gy.

A total of 6 cohorts experienced $\leq$5% RIBP with doses greater than 60 Gy, with 5 cohorts having been simulated by 3D-CT techniques. Of these 5 cohorts, 4 consisted of patients with head and neck cancer treated by IMRT technique.

Four cohorts total experienced an RIBP incidence >5% despite EQD2 doses below 60 Gy. Of these, the highest RIBP incidence was 20% observed at a bpDmax of 51 Gy in a cohort of breast cancer patients [24].

3.4. Meta-analysis

A total of 5 studies reporting RIBP effect size in relation to bpDmax were selected for meta-analysis. All included studies utilized 3D-CT planning (Table 2B). Two studies reported continuous effect sizes while the remainder had categorical dose variables; the effect sizes in the latter studies were converted to continuous represen-

Table 1
Cohort characteristics.

Characteristic	All (n = 37)	2D planned (n = 19)	3D-CT planned (n = 18)
Mean age, years (SD)*	56.9 (14.7)	54.5 (2.8)	62.9 (7.7)
Median cohort size (IQR)	67 (1 1 5)	111 (152.5)	30 (64)
Disease site (%)			
Breast	20 (54.1)	19 (1 0 0)	1 (5.6)
Head and neck	6 (16.2)	–	6 (33.3)
Lung	5 (13.5)	–	5 (27.8)
Esophagus	3 (8.1)	–	3 (16.7)
Lung and breast	1 (2.7)	–	1 (5.6)
Median latency to brachial plexopathy, months (IQR)**	7 (6)	10 (31)	7 (0.5)
Median follow up, months (IQR)***	40 (38)	66 (2 4 9)	28 (37.9)
Systemic therapy (%)			
Adjuvant	6 (16.2)	2 (10.5)	4 (22.2)
Concurrent	9 (24.3)	–	9 (50)
Concurrent or adjuvant	1 (2.7)	–	1 (5.6)

SD-standard deviation, IQR-interquartile range.
* Mean of median age of patient cohorts as presented in original studies. Missing values from 14 cohorts.
** Missing values from 19 cohorts.
*** Missing values from 8 cohorts.

tations as described previously. A single RR for each Gy increase in dose was determined for each study.

The individual continuous effect sizes of these studies and the cumulative effect size are presented in Fig. 3. [15,17,24,33,35]. The cumulative (combined) estimated RR was 1.11 (95% CI, 1.07–1.15). Given the small number and heterogeneity of included studies, the random effects model was used. Each study was weighted based on number of patients, event rate, and bpDmax range. The study by Chen et al. received the greatest weight [33]. Sensitivity analysis did not report significant change in the cumulative RR, which ranged from 1.09 (95% CI, 1.05–1.13) to 1.13 (95% CI, 1.03–1.23) with removal of Eblan et al. [15] and Amini et al. respectively [17]. Each cumulative RR value determined by sensitivity analysis was statistically significant.

Fig. 4A presents a graphical representation of the dose-effect RR for individual studies. The central dose values of each category within individual studies are shown as data points. The filled points represent the endpoint category, that is, the cohort of patients experiencing RIBP. The open points represent the patient cohort that did not experience RIBP, and are set as the reference category. This figure illustrates that, as expected, all RRs were in the direction of increasing risk with higher dose, justifying the conversion of RRs from categorical to continuous representations.

Lines corresponding to continuous effect sizes are presented in Fig. 4B, with the slopes of the lines representing the RRs. These effect estimates are presented over the range of 44 Gy-90 Gy (determined by the ranges of bpDmax reported in the included studies). The cumulative RR is 1.11 per Gy increase in bpDmax, with the 95% CI ranging from 1.04 to 1.19. The baseline risk for this line was modelled to begin at 60 Gy, corresponding to the current lowest RTOG constraint.

A funnel plot for the degree of asymmetry of individual studies around the combined RR was generated (Supplemental Fig. 1). We used trim and fill approach to adjust our estimate for asymmetry.

Table 2A
2D Planned Cohorts.

Author	Year	Disease Site	Dose per Fraction to Brachial Plexus (Gy)	Maximum Dose (Mean) to Brachial Plexus (Gy)	EQD2 (Gy)	RIBP Incidence (%)	Chemotherapy (%)
Barovic [5]	2004	Breast	2.6	52	58.2	19/140 (14)	Adjuvant (20)
Barr [25]	1987	Breast	3.4	51	65.3	6/250 (2.4)	–
Basso-Ricci [26]	1980	Breast	1.38	60	54	16/490 (3.2)	–
Johansson [13]	2002	Breast	3	49	63	8/56 (14)	–
			4	52.8	82	11/23 (48)	–
			4	51.7	80	45/71 (63)	–
Malaspina [27]	1980	Breast	4.4	44	65.12	1/15 (6.6)	–
			8.8	44	103.8	14/24 (58.3)	–
			14.7	44	155.5	18/21 (85.7)	–
Miller [28]	1998	Breast	2.6	52	58.7	2/223 (0.9)	–
Powell [14]	1990	Breast	3.1	46	55.6	17/338 (5)	–
			1.8	54	51.8	1/111 (0.9)	–
Salner [29]	1981	Breast	2	50	50	8/565 (1.4)	Adjuvant (23.8)
Stoll [3]	1966	Breast	4.25	51	74	13/84 (15)	–
			4.58	55	83.4	24/33 (73)	–
			4.55	41	62	4/25 (16)	–
			4.35	43.5	64	14/139 (10)	–
Studer [30]	2014	Breast	3.3	42.9	54	1/130 (0.7)	–
Svensson [31]	1975	Breast	3.36	57.2	72.8	45/130 (34.6)	–
Measure							
Range (Gy)			1.38–14.70	41–60	50–155.5		
Mean (Gy, SD)			4.22 (2.98)	50.5 (5.33)	71.2 (24.5)		
Median (%, IQR)						14 (38.7)	

Table 2B
3D-CT Planned Cohorts.

Author	Year	Disease Site	Radiation Technique	Dose per Fraction to Brachial Plexus (Gy)	Dmax (Mean) to Brachial Plexus (Gy)	Dmax Range to Brachial Plexus (Gy)	EQD2 (Gy)	RIBP Incidence (%)	Chemotherapy (%)
‡Amini [17]	2012	Lung	3D-CRT	2	69.7	56–82	69.7	14/90 (16)	Concurrent (90)
Chang [32]	2014	Lung	SBRT and IMRT	8.75	35	–	82.25	3/10 (30)	–
‡Chen [33]	2014	Head and Neck	IMRT	1.86	65	50–79	63.14	51/352 (14)	Concurrent (63)
Din [34]	2013	Lung and Breast	SBRT	–	–	–	70.5	9/234 (3.8)	–
‡Eblan [15]	2013	Lung	3D-CRT	2.11	78	–	79.6	5/11 (45.5)	Concurrent (80) Adjuvant (8.8)
‡Forquer [35]	2009	Lung	SBRT	8	26	6–83	61.8	7/37 (18.9)	–
‡Lundstedt [24]	2015	Breast	3D-CRT	2.04	50.9	–	51.3	38/192 (19.8)	Adjuvant (88.5)
Metcalfe [36]	2016	Head and Neck	3D-CRT	1.70	59.4	41–70	55.8	2/27 (7)	Concurrent (92.6)
Sood [37]	2017	Lung	SBRT	6.60	30.1	10–67	57.8	0/18 (0)	–
Thomas [16]	2015	Head and Neck	IMRT	2.08	72.3	49–78	74.1	0/68 (0)	–
Truong [18]	2012	Head and Neck	IMRT	1.76	58.1	46–70	55.31	0/114 (0)	Concurrent (87.7)
Yahya [38]	2016	Head and Neck	IMRT	2.75	59.8	–	71.6	0/11 (0)	Concurrent (69.2)
			IMRT	2.01	60.3	–	60.3	0/20 (0)	
			IMRT	2.00	60	–	60	0/30 (0)	
Yang [39]	2017	Cervical Esophagus	3D-CRT	2.03	60.8	–	61.2	3/26 (11.5)	Concurrent (28)
			IMRT	1.84	55.3	–	53.5	2/30 (6.7)	
			VMAT	1.90	56.9	–	55.8	1/22 (4.5)	
Yathiraj [40]	2016	Head and Neck	IMRT	2.08	62.4	–	63.4	0/67 (0)	Concurrent (75)
Measure									
Range (Gy)				1.70–8.80	30.1–78.0		51.3–92.2		
Mean (Gy, SD)				3.03 (2.31)	59.5 (14.3)		65.8 (10.9)		
Median (%, IQR)								5.6 (15.5)	

‡ Included in meta-analysis.

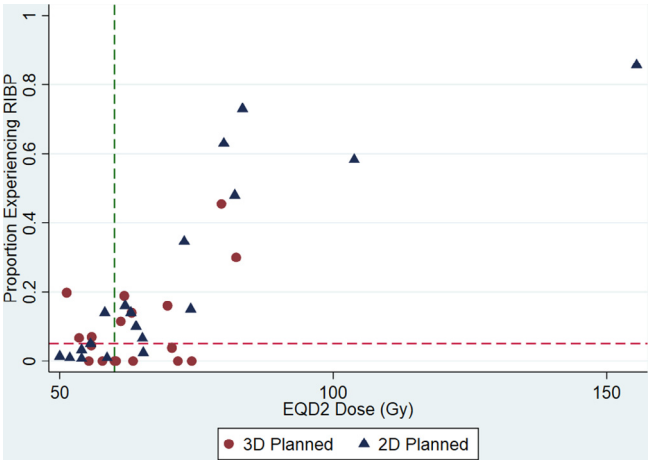

Fig. 2. Incidence of radiation induced brachial plexopathy versus absorbed plexus dose. Radiation induced brachial plexopathy (RIBP) incidence vs. EQD2 dose absorbed is plotted for all cohorts, and stratified by planning methodology. Lines denote both the current brachial plexus dose constraint of 60 Gy, as well as the 5% RIBP incidence level. Abbreviations: RIBP = radiation induced brachial plexopathy. EQD2 = equivalent dose in 2 Gy fractions.

The imputed estimate (RR 1.12; 95% CI 1.06–1.19) is similar to the cumulative effect reported in the main analysis. This suggests that although the number of studies included in this meta-analysis was limited, the resultant effect was not likely attributed to publication bias.

4. Discussion

Previous dose tolerance guidelines derived their recommendations from a handful of cohort studies [6,41]. Our study comprehensively reviewed all existing literature that describes RIBP incidence within patient cohorts. We identified 25 studies with 37 unique patient cohorts that reported radiotherapy dose to the brachial plexus and subsequent incidence of RIBP. We found that in cohorts reporting<5% incidence of RIBP, the EQD2 plexus dose was 60 Gy or less in 62.5% of the cohorts, and under 66 Gy in 75% of cohorts.

As expected, this finding is consistent with current brachial plexus dose tolerance constraints. The original brachial plexus dose tolerance was Dmax = 60 Gy as defined by Emami [6]. Current RTOG trial dose constraints for the brachial plexus are 60 Gy (RTOG 0412, 0435, 0522) or 66 Gy (RTOG 0615, 0617) [10,16,42,43] in conventional dose fractionation. However, the study sheds light on some important issues in the determination of plexus tolerance.

It should be noted that 19 of 36 included cohorts (53%) consisted of patients planned with 2D techniques. These early studies treated exclusively breast cancer patients. Non-conformal radiotherapy planning and delivery lack the dosimetric accuracy and

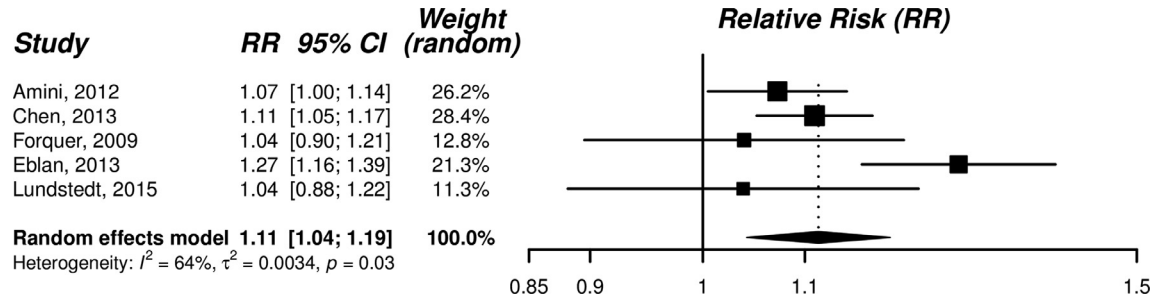

Fig. 3. Individual Study and Overall Relative Risk of Relationships between Brachial Plexus Maximum Dose and Brachial Plexopathy Risk. The size of each data maker represents the weighting factor ($1/SE^2$) assigned to the study. For the combined result, the width of the diamond represents the 95% confidence interval of the summated results.

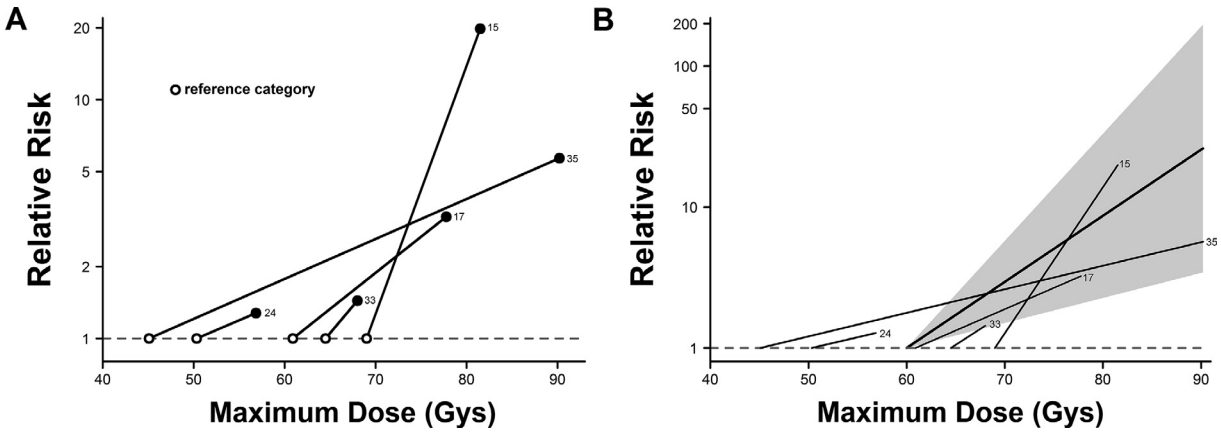

Fig. 4. Relative Risk of Radiation Induced Brachial Plexopathy in Relation to Brachial Plexus Maximum Dose. (A) The relationship between brachial plexus maximum dose and RIBP risk are denoted for the 5 individual studies. Data points correspond to median values of the endpoint category (filled) and reference category (open) respectively. Numbers correspond to the references for original studies. (B) RR values are converted to continuous estimates per Gy increase of dose, which is represented by the slope. The bolded line represents the weighted cumulative average of the individual RRs, with the shaded region representing the 95% confidence interval. *Abbreviations*: RR = relative risk; RIBP = radiation induced brachial plexopathy.

precision of modern 3D techniques and leads to higher toxicity rates and worse disease control [44,45]. The risk of inter-fractional target volumes shifts and potential over dosage to structures such as the brachial plexus is higher. Our data shows higher proportions of RIBP in cohorts treated with non-IGRT techniques.

In the present study, all head and neck cohorts with a bpDmax $\geq$60 Gy resulted in an RIBP incidence of 0%. All patients were treated with IMRT techniques. The mean Dmax of the plexus doses ranged from 60.3 to 72.3 Gy [16,18,38,40]. The brachial plexus tolerance has been thought to be greater in patients receiving head and neck radiotherapy. Postulated reasons for this discrepancy include shorter patient survival, smaller plexus volume irradiated, and less field overlap hotspots in these patients in comparison to breast cancer studies from which brachial plexus constraints are mainly based upon. Adjuvant treatments such as surgery and chemotherapy may also contribute to this observation [46].

Determination of potential discrepancies in plexus tolerance is critical as treatment doses often approach 70 Gy in head and neck patients. Chen et al. found that with IMRT, higher plexus doses were measured compared to 3D conformal plans [47]. IMRT and VMAT are the current standard radiotherapy technique in the treatment of head and neck malignancies. Although these techniques allow for better dose conformity, they pose an increased risk of hotspots [18]. The factors influencing brachial plexus tolerance, particularly dosimetric and volumetric variables, warrant further evaluation.

Meta-analysis of the studies that reported plexus dosimetry and RIBP effect size resulted in a log-linear relationship between increasing bpDmax and RIBP relative risk; each 1 Gy increment was associated with a 1.11 RR increase in RIBP. Assuming a RIBP risk of 5% at a bpDmax of 60 Gy based on original Emami guidelines [6], at 70 Gy, this model would predict a risk of 14.2% ($0.05 \times 1.11^{(70-60)} = 0.142$). This model can serve as a guiding tool in the quantification of RIBP risk over the range of bpDmax given in Fig. 4B.

We acknowledge certain limitations of our analysis. First, the inter-patient anatomic heterogeneity and inter-observer differences in plexus delineation introduces uncertainty in the reported brachial plexus absorbed doses. Sood et al. reported significant variability in brachial plexus dose in SBRT plans for 31 patients with apical lung tumors. The median maximum dose was 15.8 Gy, but with a broad range of 1.7–66.5 Gy [37]. Furthermore, our study includes a significant proportion of patients planned with 2D techniques, which results in further plexus dose variability and uncertainty within each cohort. These uncertainties are unfortunately characteristic of the study data and unavoidable. Central measures of the absorbed plexus dose remain the most reasonable parameter in comparing cohorts. Novel, anatomically validated brachial plexus contouring guidelines may serve to provide more accurate and precise dosimetric data in future studies [48].

Second, our analysis did not investigate factors that may modify RIBP risk. Several cohort studies have reported evidence suggesting an increased risk of RIBP in patients receiving chemotherapy. Olsen et al. found that the incidence of RIBP in breast cancer patients receiving CMF chemotherapy was 20% compared to only 4% in the tamoxifen arm ($p = 0.01$) [49]. Similarly, another study of

breast cancer patients found an RIBP incidence of 4.5% versus 0.6% in the chemotherapy and non-chemotherapy arms respectively ($p < 0.0001$) [50]. In the present study, chemotherapy was delivered to patients in 16 of 36 included patient cohorts. Concurrent or adjuvant chemotherapy was given in 4 of the 5 included meta-analysis studies (Table 2B).

Extensive surgery in the peri-plexal region has also been shown to increase the risk of RIBP [51]. The majority of included cohorts in our study involved breast cancer patients, a proportion of which may have undergone axillary surgery. Caution must be taken when extrapolating tolerance constraints to patients who have had these adjunct therapies.

The dose fractionation may also influence the risk of developing RIBP. Like other normal tissues, the lower alpha/beta ratio of the brachial plexus suggests increased tissue sensitivity to larger fraction sizes. A review of breast cancer studies found that the risk of RIBP was <1% when fractions sizes ranged between 2.2 and 2.5 Gy and total dose did not exceed 40 Gy. With fraction sizes between 2.2 and 4.58 Gy and total dose up to 60 Gy however, the RIBP incidence ranged from 1.7 to 73% [52]. Although all bpDmax values in the present study were converted to corresponding EQD2 doses, RIBP risk may in practice, be higher in cohorts treated with hypofractionation than estimated by our model. The present study contains too few cohorts to account for this hypothesis in our predictive model.

Third, follow-up times were heterogeneous amongst individual cohorts. Studies with longer follow-up may capture more RIBP events. This is unfortunately a bias inherent in the nature of a systematic review.

Fourth, our model assumes a log-linear relationship between bpDmax and RIBP risk. This assumption is supported by the individual study trends (Fig. 4A). It is however, limited to the dose ranges given by the reference studies. Extrapolation of risk beyond this range must be approached with caution, albeit rare that brachial plexus doses should exceed this range.

The brachial plexus, like other neuronal structures, has been classically described as a serial organ. The risk of toxicity is defined in relation to bpDmax. This is the parameter used in current trial dose constraints, and is also the measure used in our analysis. However, emerging evidence exists that there is a volume effect associated with the brachial plexus. Lundstedt et al. found an absolute risk increase of 12% in breast cancer patients receiving V_{40} >13.5 cm^3 compared to smaller volumes [24]. Similarly, Chen et al. found a significant increase in RIBP incidence when V_{70} >10% [33]. We did not perform volumetric analysis in our study given the heterogeneity of data. Lower irradiation volumes may be an explanatory factor for the lower rates of RIBP observed in head and neck patients.

Lastly, our analysis includes observational rather than randomized data. However, it is unlikely that randomized trials assessing dose tolerances will ever be conducted. There were only 5 studies eligible for inclusion in the meta-analysis. Therefore, a random effects model was required, and the resultant cumulative effect size was associated with a wide confidence interval. This again illustrates the need for additional prospective, dosimetric study data to further refine our model.

5. Conclusion

A review of the available literature suggests that current brachial plexus constraints of 60–66 Gy are safe, albeit a significant proportion of the evidence is based on obsolete 2D techniques. Meta-analysis of contemporary studies reports a log-linear model associating bpDmax with RIBP risk; each 1 Gy increase is associated with a 1.11 RR increase in RIBP. The results of this model can inform the therapeutic ratio for dose escalation, but are limited by, amongst other factors, the quality and heterogeneity of studies. There is a need for further prospective studies investigating dosimetric parameters to better inform brachial plexus constraints.

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Declaration of Competing Interest

None.

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Appendix A. Search strategies for each database

Database	Search
Medline	1. Brachial Plexus/ 2. Brachial Plexus Neuropathies/ 3. brachial plex*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 4. 1 or 2 or 3 5. radiation dosage/ or dose–response relationship, radiation/ 6. Radiation Injuries/ 7. exp Radiotherapy/ 8. radiation.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 9. radiotherap*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] 10. brachytherap*.mp. [mp = title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

(*continued on next page*)

Appendix A. Search strategies for each database (*continued*)

Database	Search
	11. radiotherapy.fs.
	12. radiation effects.fs.
	13. or/5–12
	14. 4 and 13
Embase	1. exp brachial plexus/
	2. exp brachial plexus neuropathy/
	3. brachial plex*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
	4. 1 or 2 or 3
	5. exp cancer radiotherapy/
	6. exp radiation injury/
	7. exp radiation dose/
	8. radiation.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
	9. radiotherap*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
	10. brachytherap*.mp. [mp = title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]
	11. radiotherapy.fs.
	12. or/5–11
	13. 4 and 12
CINAHL	S1 (MH "Radiotherapy")
	S2 (MH "Radiation Dosage")
	S3 (MH "Radiation Injuries")
	S4 "radiotherap*"
	S5 "brachytherap*"
	S6 S1 OR S2 OR S3 OR S4 OR S5
	S7 (MH "Brachial Plexus")
	S8 (MH "Brachial Plexus Neuropathies")
	S9 "brachial plex*"
	S10 S7 OR S8 OR S9
	S11 S6 AND S10

Appendix B. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2019.06.006.

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